DOCKET NO.: ISIS-4502 PATENT

Application No.: 08/078,768
Office Action Dated: June 17, 2003

This listing of claims will replace all prior versions, and listings, of claims in the application.

## **Listing of Claims:**

64. (Previously presented) A method of selectively inhibiting the expression of a target protein in a cell producing messenger ribonucleic acids encoding the target protein and other proteins without inhibiting the expression of the other proteins, said method comprising the steps of:

- (a) synthesizing an oligonucleotide having a base sequence substantially complementary to a subsequence of a messenger ribonucleic acid said subsequence coding for the target protein,
  - (b) introducing the oligonucleotide into the cell; and,
- (c) hybridizing the oligonucleotide to the subsequence of the messenger ribonucleic acid to inhibit the expression of the target protein.
- 65. (Previously presented) The method of claim 64 wherein the entire sequence of the oligonucleotide is complementary to the subsequence of a messenger ribonucleic acid coding for the target protein.
- 66. (Previously presented) The method of claim 64 wherein the oligonucleotide is at least 14 bases in length.
- 67. (Previously presented) The method of claim 64 wherein the oligonucleotide is about 23 bases in length.
- 68. (Previously presented) The method of claim 64 wherein the oligonucleotide is between 14 and 23 bases in length.
- 69. (Previously presented) The method of claim 64 wherein the messenger ribonucleic acid is viral.

DOCKET NO.: ISIS-4502 PATENT Application No.: 08/078,768

Office Action Dated: June 17, 2003

70. (Previously presented) The method of claim 64 wherein the messenger ribonucleic acid encodes a hormone.

71. (Previously presented) The method of claim 64 wherein the oligonucleotide is stabilized to inhibit degradation by nucleases.

72. (Previously presented) The method of claim 64 wherein the oligonucleotide is an oligodeoxynucleotide.

73. (Previously presented) A method of selectively inhibiting the expression of a target protein in a cell producing messenger ribonucleic acids encoding the target protein and other proteins without inhibiting the expression of the other proteins, said method comprising the steps of:

selecting a synthetic oligonucleotide that has enhanced resistance against nuclease enzymes and has a base sequence substantially complementary to a subsequence of a messenger ribonucleic acid of said cell, said subsequence coding for the target protein,

introducing said synthetic oligonucleotide into the cell, and

hybridizing said synthetic oligonucleotide to the subsequence of the messenger ribonucleic acid to inhibit the expression of the target protein.

- 74. (Previously presented) The method of claim 73 wherein said synthetic oligonucleotide is between 14 and about 23 bases in length.
- 75. (Currently amended) A method of selectively inhibiting the expression of a target protein in a cell producing messenger ribonucleic acids encoding the target protein and other proteins without inhibiting the expression of the other proteins, said method comprising the steps of:

selecting a synthetic oligonucleotide that has enhanced resistance against nuclease enzymes and has a base sequence substantially complementary to a subsequence of a messenger ribonucleic acid of said cell, said subsequence coding for the target protein, and

DOCKET NO.: ISIS-4502 PATENT Application No.: 08/078,768

Office Action Dated: June 17, 2003

introducing said synthetic oligonucleotide into the cell at a temperature between 0°C and 80°C to hybridize said synthetic oligonucleotide to the subsequence of the messenger ribonucleic acid.

76. (Previously presented) The method of claim 75 wherein said synthetic oligonucleotide is between 14 and about 23 bases in length.

## 77. (Cancelled)

78. (Previously presented) A method of selectively inhibiting the expression of a target protein in a cell producing messenger ribonucleic acid encoding the target protein, said method comprising the steps of:

selecting a base sequence substantially complementary to said messenger ribonucleic acid of said cell coding for the target protein,

providing a synthetic oligonucleotide that is stabilized against *in vivo* degradative enzymes, said synthetic oligonucleotide having said selected base sequence, and

introducing said synthetic oligonucleotide into the cell whereby said synthetic stabilized oligonucleotide hybridizes to the subsequence of the messenger ribonucleic acid.

- 79. (Previously presented) The method of claim 78 wherein said synthetic oligonucleotide is between 14 and about 23 bases in length.
- 80. (Previously presented) A method of selectively inhibiting the expression of a target protein in a cell producing messenger ribonucleic acids encoding the target protein, said method comprising the steps of:

selecting a plurality of base sequences that are complementary to said messenger ribonucleic acid,

providing a synthetic oligonucleotide corresponding to each of said base sequences, selecting a preferred one of said synthetic oligonucleotides for inhibition of the expression of said target protein in a cell, and

using said selected oligonucleotide for inhibition of said target protein in cells.

Page 4 of 9

DOCKET NO.: ISIS-4502 Application No.: 08/078,768 Office Action Dated: June 17, 2003

81. (Previously presented) The method of claim 80 wherein said synthetic oligonucleotides are oligonucleotides stabilized against *in vivo* degradative enzymes.

- 82. (Previously presented) The method of claim 80 wherein said selected synthetic oligonucleotide is between 14 and about 23 bases in length.
- 83. (Previously presented) The method of claim 80 further comprising the step of synthesizing bulk amounts of said selected oligonucleotide for inhibition of said target protein *in vivo*.

